DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
One Montvale Avenue Stoneham, MA 02180 (781) 587-7500 Fax:(781) 587-7556 Industry Information: www.fda.gov/oc/industry	10/10/2012 - 11/09/2012* FEI NUMBER 3005881167

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

TO: Gregory A. Conigliaro, Vice President and General Manager

FIRM NAME	STREET ADDRESS
Ameridose, LLC	201 and 205 Flanders Rd
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Westborough, MA 01581-1032	Sterile Drug Manufacturer

3. Your firm's Quality unit failed to investigate a trend of complaints associated with Midazolam for low potency / lack of effect.

   The Table below summarizes this information:

Date Received	Complaint	Midazolam Lot	Additional Information
02/23/2012	AC12120	1222011@157	Made reference to an unspecified adverse event and the involvement of more than one patient being affected.
03/02/2012	AC12133*	02222012@654 02172012@248 02122012@1	Made reference to more than one patient being affected and that a few physicians were concerned about potency.
03/08/2012	AC12144*	03032012@39 02122012@1 01312012@42	Made reference to reports from more than one anesthesiologist about product response.
03/26/2012	AC12186	02112012@245	Made reference to more than one patient being affected.
04/02/2012	AC12195	03282012@674	Made reference to lack of effect despite using the max allowable dose.
05/09/2012	AC12244	05012012@41	Made reference to more than one patient being affected and reports from more than one nurse.
09/06/2012	AC12427	08272012@43	Accompany documentation states

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		08092012@786	"they have had three (3) pediatric patients require extremely large doses for relief".

* Complaints AC 12133 and AC12144 reference the same lot (02122012@1) and were received from independent customers. The final, Quality approved reports state "No trends associated with this lot".

4. Your firm failed to investigate the following complaints as they were defined as "non-complaints" by your firm's Quality unit:

Drug	Date Received	Lot	Description
Norepinephrine	09/28/2012	09242012 @553	Concerns related to potency; related to an adverse event.
Succinylcholine	09/17/2012	06212012 @309	Concerns related to potency; associated with an adverse event.
Meperidine	08/31/2012	08272012 @598	Complaint stated "bubbles of drug along the rim, outside of the drug reservoir"; sterility concerns
Fentanyl Bupivacaine	09/07/2012	07132012 @472	Under-filled product concerns.
Nalbuphine	08/30/2012	08282012 @978	Syringe fill volume concerns.

Furthermore, all of these complaint files were reviewed and deemed acceptable by your Quality Unit.

E. Your firm failed to investigate aberrant peaks in HPLC chromatograms associated with finished sterile product. This includes the following:

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1. On 03/23/2012, a Diltiazem, lot 02152012@318 complaint sample (AC12165) was evaluated by HPLC analysis to determine potency. The chromatograms associated with the sample exhibited several unknown peaks when compared to the control (reference standard). Additionally, the complaint was associated with a "patient response" in which the recipient of the drug "developed a phlebitis-type reaction with tracking up the veins". The unknown peaks have not been investigated nor have they been evaluated with respect to the "patient response".

2. On 08/08/2012 a Ropivacaine, lot 07022012@344 complaint sample (Complaint AC12382) was evaluated by HPLC analysis to determine potency. The chromatograms associated with the sample exhibited an unknown peak when compared to the control (reference standard). Additionally, the complaint was associated with a "patient response" in which the product "was not giving relief to 4 patients". The unknown peak has not been investigated nor has it been evaluated with respect to the "patient response".

3. The HPLC chromatograms used to evaluate potency for Morphine stock lots S09252012@381, S09252012@382, and S09252012@448 exhibited an unknown peak when compared to the control (reference standard). The lots were released on 09/27/2012 for further manufacture. The unknown peak has not been investigated nor has it been evaluated with respect to patient risk.

OBSERVATION 4

Procedures designed to prevent microbiological contamination of drug products purporting to be sterile do not include adequate validation of the sterilization process.

Specifically,

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A. The sterile technique qualification (media fills) do not represent your routine operating conditions and does not evaluate worst-case activities that can provide a challenge to manual aseptic operations. Specifically,

1. Your media fills do not challenge the maximum number of times drug product lots can be filled from sterile stock solutions or the maximum number of units filled without increasing the risk of contamination of the manufactured sterile drug product. For example stock solutions can be stored and used to fill over a course of (b) (4) days. Stock solution of Ropivacaine 0.2% lot S09132012@312 was used to fill approximately (b) (4) final products lots in 09/2012.

2. Your aseptic process validation does not challenge representative container closure systems currently used at your facility that represents a worst case challenge. For example, your firm performs media fill studies with (b) (4) bags when the following sizes: 25mL, 50mL, 150mL, 250mL, 500mL, 1000mL, 3000mL and 4000mL bags are used during routine production.

3. Your media fills do not simulate aseptic manufacturing operations that incorporate worst-case activities and conditions that provide a challenge to aseptic operations. For example: maximum number of personnel and their activities, and an evaluation of critical routine and non-routine interventions (e.g. the continuous entering and exiting of the class 100 hoods used in the manufacture of sterile drug products.)

B. Sterile Filtration has not been validated for its intended use. For example:

1. Bacterial retention challenge has not been performed for product contac (b) (4) (b) (4) (b) (4) filters used to sterile filter injectable drug products intended for patient use for example Fentanyl, Ropivacaine, etc.

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2. (b) (4) is recommended to be use for general laboratory use and not intended for direct patient care applications.
3. The firm does not have the data, procedures, and controls to assure that additional rounds of filtration do not adversely impact product. Your firm re-filtered, at least one time, all sterile stock solutions lots involved in the sterility failures before releasing final drug product lots for patient use.

OBSERVATION 5

There are no written procedures for production and process controls designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess.

Specifically,

Your firm utilizes a (b) (4) pump to manually administer drug product to individual units from stock solutions during the processing of sterile finished products. The number of pumps ("pump count") is not routinely reconciled with the total number of units manufactured to ensure labeled potency. This includes the following lot which was also associated with low potency complaints and a "patient response":

For example: Midazolam, lot 02122012@1 (released on 02/12/2012) which is also associated with lack of effect / low potency complaints AC12133 (approved by Quality on 03/12/2012) and AC12144 (approved by Quality on 03/16/2012).

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OBSERVATION 6

Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not established, written, and followed.

Specifically,

A. The environmental monitoring and conditions of the aseptic core are deficient for the following reasons:

1. Gowning used to manufacture sterile drug products is inadequate:

   a. Personnel gowns, eye-protection and gloves are not sterile. In addition gowns are only laundered and re-used for up (b) (4) before they are sent for cleaning.

   b. Personnel exposed foreheads were observed as part of their gowning procedures. These operators can work inside the open-faced class 100 hoods in the manufacture of sterile injectable drug products.

2. Environmental monitoring of the class 100 (b) (4) hoods in not performed in association with daily operations. Sterile drug products are aseptically manipulated in these hoods as part of daily operations. However, environmental monitoring for non-viable particulates is performed ever (b) (4) and monitoring for viable particulates is performed (b) (4) in the class 100 hoods.

3. The firm failed to perform environmental monitoring during the manual aseptic connections from the stock solutions or during the manual filling of sterile injectable drug products.

4. Personnel monitoring is limited to the assessment of the manufacturing technician's

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fingers and this sampling is done only (b) (4). Other critical areas such as forehead, forearms, chest and shoulders are not monitored.

OBSERVATION 7

The accuracy, sensitivity, specificity, and reproducibility of test methods have not been established and documented.

Specifically,

Method validation and performance qualification for the (b) (4) to test the sterility of sterile injectable drug products manufactured is inadequate for the following reasons:

1. Your firm did not adequately execute a side by side comparison of this method with compendia sterility method as required in your validation. There is no justification for comparing the (b) (4) results with a (b) (4) (b) (4) when the current USP method requires a 14 day incubation.

2. The population for the challenge microorganisms used in validation was never evaluated.

3. The method was validated by (b) (4) of the challenge microorganisms. Furthermore, there is no data to support that the lowest level of detection was challenged during validation.

4. There is no adequate data to support the reproducibility of the (b) (4) method. Specifically, on numerous occasions the firm performed multiple (b) (4) of the same sample

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rendering all negative results in the firs(b) (4) and showing viability in the following(b) (4) All samples are(b) (4) s part of routine production.

OBSERVATION 8

The operations relating to the manufacture, processing, and packing of penicillin are not performed in facilities separate from those used for other drug products for human use.

Specifically,

There is no data to support that the firm's processing procedures will not increase the risk of cross-contamination between products. For example: the firm manufactures beta-lactam drug products in a non dedicated facility where sterile injectable drug products are manufactured. Your firm's employees can manufacture beta-lactam and non beta-lactam products in any hoods interchangeably. Furthermore, the firm does not test/assess for the presence of beta-lactams in other sterile manufactured drug products at building(b) (4)

OBSERVATION 9

Buildings used in the manufacturing, processing, packing, and holding of a drug product are not maintained in a good state of repair.

Specifically,

A. The firm failed to perform a microbiological assessment after penetrating leaks were found in building(b) (4) dripping above the clean room in 06/2012. During the inspection 10/2012 we observed totes placed in the location of the penetrating leaks containing water. There is no documented evidence that the leaks were permanently corrected.

B. Walls were observed to be cracked, corroded, and covered with what appeared to be adhesive material in Room A of Building(b) (4), where sterile drug products are aseptically prepared.

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